UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,239	09/22/2006	Lutz Hilbrich	1/1461PCT	2608

28501 7590 06/29/2007

MICHAEL P. MORRIS
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1609	

MAIL DATE	DELIVERY MODE
06/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,239	HILBRICH ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/02/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/02/05 and 2/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claim(s) 1-9 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the risk of stroke or secondary stroke, does not reasonably provide enablement for preventing the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention.

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method and composition comprising dipyridamole or a pharmaceutical acceptable salt thereof, in combination with acetylsalicylic acid and an angiotensin II antagonist for preventing or reducing the risk of stroke or secondary stroke in a patient in need thereof (*see* instant Claims 1, 3 and 5). The specific angiotensin II antagonist recited in the instant claims is telmisartan (*see* instant Claims 2, 4 and 6).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

There is a known unpredictability in the art when engaging in the prevention of stroke or secondary stroke. While risk factors, such as hypertension, diabetes mellitus, alcohol consumption, obesity, smoking, age, gender, race, heart disease or other diseases, such as polycythemia, sickle cell disease, migraine or CNS vasculitis, are acknowledged in the art to be definite or presumed contributors to the development of

such a disorder (*see* Cecil's Textbook of Medicine, p.2105-2106, "Risk Factors and Primary Prevention Therapies"), the presence of any one or more of these risk factors does not necessarily guarantee the development of such a condition. Although there are efficacious therapies, such as antiplatelet drugs or anticoagulants used to treat cardiovascular conditions associated with the incidence of stroke (e.g., atrial fibrillation or myocardial infarction; *see* Cecil's, Table 470-3, p.2105), that can be used for the relatively predictable treatment of patients exhibiting risk factors for stroke, the use of any one or more of these therapies does not necessarily guarantee that the prevention of such a condition will be achieved. Therapies known in the art are primarily associated with behavioral modifications, such as smoking cessation, obesity and diet control or moderation of alcohol consumption, and are recognized to reduce the risk of developing stroke (*see* Cecil's, p.2105-2106). While pharmaceutical combinations of clopidogrel and ASA and dipyridamole and ASA have shown efficacy in reducing the risk of recurrent stroke, such is not recognized to allow for the absolute prevention of such a condition (*see* Cecil's, p.2106, "Stroke and TIA"). Thus, the art does not recognize any therapeutic modality guaranteed to prevent stroke or secondary stroke and the outcome of treatment with known pharmaceutical therapies or behavioral therapy is not recognized to provide absolute prevention of such a condition.

(5) The relative skill of those in the art:

The level of skill in this art is high and is at least that of an experienced M.D. or Ph.D.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for reducing the risk of stroke or secondary stroke in a patient in need thereof.

However, the specification does not provide guidance for the prevention of stroke or secondary stroke in a patient in need thereof.

Applicant has merely disclosed that by administering the claimed active composition in a patient who has experienced, or is at risk for experiencing a stroke, one may prevent the occurrence of such a condition in a patient. Based on the discussion above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed active agent(s) could be employed to accomplish the prevention of stroke in a predictable manner.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the prevention of stroke or secondary stroke and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 101 and 35 USC § 112, Second Paragraph

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 provides for the use of dipyridamole or a pharmaceutically salt thereof in combination with acetylsalicylic acid and an angiotensin II antagonist for the manufacture of a pharmaceutical composition for stroke prevention or reducing the risk of stroke or secondary stroke in a patient, and Claim 6 provides for the use of Claim 5 wherein the angiotensin II antagonist is telmisartan, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 5 and 6 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 0130353 (Eisert) in view of WO 0115673 (Schoelkens et al.), Hervey, et al and Cecil's Textbook of Medicine, 21st Edition.

Eisert expressly discloses compositions of dipyridamole in combination with acetylsalicylic acid (ASA) or dipyridamole in combination with other cardiovascular therapies, such as ACE inhibitors, angiotensin II antagonist (e.g., telmisartan, *see* WO

0130353, page 10, 2nd paragraph), Ca-antagonists or lipid-lowering agents such as the statins (*see* WO 0130353, page 5, first paragraph), each combination of which may be employed for the treatment of fibrin-dependent microcirculation disorders (*see* WO 0130353, paragraph bridging pages 5-6, page 7, and page 8, paragraphs 1-3), including e.g., arterial hypertension, atherosclerosis, ischemic or coronary heart diseases, diabetic retinopathy or vascular dementia (*see* WO 0130353, claim 3 bridging pages 13-14).

Eisert does not expressly teach one single combination of dipyridamole, acetylsalicylic acid and an angiotensin II antagonist and Eisert does not specify a method of reducing the risk of stroke or secondary stroke in a patient in need thereof.

Hervey et al. teach a method of using a composition consisting of dipyridamole and aspirin for protection against stroke, secondary stroke and transient ischemic attack (*see* Abstract and table on page 469). They also teach that the antiplatelet activity of dipyridamole and aspirin are through different mechanisms, namely, dipyridamole by inhibiting phosphodiesterase and the uptake of adenosine, and aspirin by inhibiting cyclo-oxygenase and limiting production of thromboxane A_2 (*see* page 470, heading labeled "Pharmacodynamic Profile).

Schoelkens et al. teach, *inter alia,* the use of an inhibitor of the renin-angiotensin system, which include inhibitors of angiotensin converting enzyme (ACE) and angiotensin II type 1 receptor antagonists, in the treatment of stroke (*see* page 1, lines 6-12 and 16-21). They also teach the use of the specific angiotensin II antagonist, telmisartan (*see* page 13, claim 8).

While Eisert does not particularly teach a method of reducing the risk of stroke or secondary stroke using a dipyridamole, acetylsalicylic acid and an angiotensin II antagonist composition, Eisert expressly teaches that the disclosed pharmaceutical compositions comprising these three components may be employed in a method of treating fibrin-dependent microcirculation disorders **or of disease states where such microcirculation disorders are involved** (emphasis added; *see* page 5, paragraph 3-page 6, paragraph1). It was well known in the art at the time of the invention that disorders such as arterial hypertension or atherosclerosis were risk factors and causes of stroke (*see* Cecil's Textbook of Medicine, page 2102 "Atherosclerosis" and page 2105 "Risk Factors and Primary Prevention Therapies-Definite Genetic and Lifestyle Risk Factors. Hypertension"). Since Eisert defines atherosclerosis and hypertension as microcirculation disorders and Cecil's Textbook of Medicine implicates such conditions as risk factors and causes of the development of stroke, it would have been obvious that the teachings of Eisert, specifically the disclosure of "disease states where such microcirculation disorders are involved" (i.e., stroke per Cecil's Textbook of Medicine) are clearly indicative of a method of reducing the risk of stroke via the treatment of disorders associated with such a condition (i.e., hypertension or atherosclerosis). Furthermore, while the Examiner notes that the teachings of Eisert in view of Cecil's Textbook does not expressly teach reducing the risk of secondary stroke, it would have been obvious to a person of ordinary skill in the art at the time of the invention that treatment methods relevant to reducing the risk of primary stroke would be viable treatment methods for reducing the risk of secondary stroke, since it would be

reasonably expected, absent factual evidence to the contrary, that the etiology of a secondary stroke would not differ drastically from the etiology of a primary stroke. Additionally, Hervey et al. teach the use of the combination of dipyridamole and aspirin for the treatment of stroke, secondary stroke, and transient ischemic attacks (supra), and Schoelkens et al. teach the use of telmisartan in the treatment of stroke (supra).

While Eisert does not expressly teach one single combination of dipyridamole, acetylsalicylic acid and an angiotensin II antagonist, the combination of all three agents in light of the teachings of Eisert would have been *prima facie* obvious to the artisan of ordinary skill. Such a person would have been motivated to combine all three agents into a single composition because the combination of dipyridamole and acetylsalicylic acid and the combination of dipyridamole and an angiotensin II antagonist were each known to have efficacy in the treatment of fibrin-dependent microcirculation disorders or of disease states where such microcirculation disorders are involved (*see* Eisert, page 5, paragraph 3 to page 6, paragraph 1, page 9, paragraph 3, and page 10, paragraph 2). Motivation to administer all three compounds together flows logically from the efficacy demonstrated in the prior art of the administration of combinations of compositions or compounds used for the same therapeutic objectives. In Eisert, the combination of dipyridamole with acetylsalicylic acid and the combination of dipyridamole with an angiotensin II antagonist (e.g., telmisartan) have each been show to be effective in the treatment of fibrin-dependent microcirculation disorders (supra). In the absence of evidence to the contrary, it is generally *prima facie* obvious to use in

combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Furthermore, the combination of all three agents into a single formulation would not only have been reasonably expected to achieve an additive effect in the treatment of such microcirculation disorders, but would also have improved patient compliance with a regimen requiring the regular intake of multiple pharmaceutical compositions by administering all three in a single formulation.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

9. Claims 3 and 4 of this application conflict with Claims 8 and 9 of Application No. 10912966 and Claims 1 and 2 of this present application conflict with Claims 20 and 22 of Application No. 11478184. 37 CFR 1.78(b) provides that when two or more

applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. Claims 3 and 4 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 8 and 9 of copending U.S. Patent Application No. 10/912966. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

12. Claim 1 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 20 of copending U.S. Patent Application No. 11478184. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 3 and 4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending U.S. Patent Application No. 11/478184. Although the conflicting claims are not identical, they are not patentably distinct from each other because the difference between the presently claimed subject matter and the subject matter of the copending claims is: the copending claims specify a therapeutically effective amount of the agents of the pharmaceutical compositions claimed by both applications and they specify telmisartan, or a salt or polymorph thereof.

Whereas Claims 3 and 4 of the present application do not specify a therapeutically effective amount of the composition, it would be obvious to one of ordinary skill in the art to administer the composition in a therapeutically effective amount. Additionally, instant Claim 4 does not specify that telmisartan may be in the

form of its salt or polymorph thereof it would be obvious to one of ordinary skill in the art to use the form to telmisartan which had the best desired bioavailability properties.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. Claims 1-6 are rejected.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on M-F 7:30 A.M. - 5:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GP

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600